Immunization in children with chronic renal failure: a practical approach

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REVIEW

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Immunization in children with chronic renal failure: a practical approach

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Abstract The prevention of systemic viral and bacterial infections by effective vaccination represents an essential task of pediatric nephrologists caring for children with chronic renal failure (CRF) undergoing renal transplantation (RTPL) with life-long immunosuppression. This review addresses three issues: risk of vaccine-preventable diseases, safety, immunogenicity, and clinical efficacy of available vaccines, and implementation of immunization guidelines. Infections (including vaccine-preventable infections) represent the leading cause of morbidity and mortality in children on dialysis and after RTPL. Vaccination in children with CRF and after RTPL is safe and does not cause reactivation of an immune-related renal disease or rejection after RTPL. Children with CRF generally produce protective serum antibodies to primary vaccinations with killed or component vaccines and live virus vaccines; some children on dialysis and after RTPL may not respond optimally, requiring repeated vaccination. Proof of vaccine efficacy is absence of disease, which can only be confirmed in large cohort studies. A few observational studies provide evidence that vaccination has contributed significantly, at least in the western hemisphere, to the low prevalence of vaccine-preventable diseases among children with CRF. Close cooperation between the local pediatrician/practitioner and the pediatric nephrologist is essential for successful implementation of the vaccination schedule.

Keywords Vaccination · Safety · Immunogenicity · Efficacy · Chronic renal failure · Dialysis · Renal transplantation

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Introduction

The prevention of systemic viral and bacterial infections by effective vaccination represents an essential part of a pediatrician's work. This task is particularly important for those specialists caring for children with chronic renal failure (CRF) that eventually undergo renal transplantation (RTPL) with life-long immunosuppression. The following issues will be addressed in children with CRF on conservative treatment, on long-term dialysis, and after RTPL: (1) the risk of vaccine-preventable diseases, (2) the safety, immunogenicity, and clinical efficacy of available vaccines, and (3) the implementation of the recommended immunization guidelines.

Immunization recommendations—for healthy and immunocompromised children—vary between countries and possibly even between different health authorities depending on the local population base. Recommendations for immunization in children with CRF follow the primary vaccine schedules [1, 2, 3]; in addition, children with CRF should be protected against varicella, influenza, hepatitis B, and *Streptococcus pneumoniae* if not included in their primary schedule. Specific guidelines and recommendations for children with CRF have continuously been updated [4, 5, 6, 7, 8, 9, 10]. Most recommendations contain a commentary stating that the "guidelines are derived from small or controversial studies, or represent the opinion of the group of experts grading the evidence on level C" [10]. The implementation of these guidelines varies substantially in different pediatric renal centers [11].

Children with CRF on conservative treatment or dialysis have no significant immune impairment except in a few clinical conditions, e.g., nephrotic syndrome and systemic lupus erythematosus. Some children on peritoneal dialysis have hypogammaglobulinemia (total IgG or IgG subclasses) either due to loss of IgG in the dialysate or due to impaired IgG production [12, 13, 14, 15, 16, 17, 18, 19]. After RTPL, immunosuppressed infants and young children without specific protection—either after immunization or wild type infection—are at risk from

benign childhood infections that can be severe and life threatening [20, 21].

The risk of vaccine-preventable diseases

Publications from large registries or single centers show that infections represent the leading cause of morbidity and mortality in children on dialysis and after RTPL [20, 21, 22, 23, 24, 25, 26]. Most reports are limited and do not provide precise information regarding the specific pathogens. Thus, epidemiological data on incidence and prevalence of vaccine-preventable infections in children with CRF are scarce [21, 27, 28, 29, 30, 31].

Whereas hepatitis B has become very rare in some western countries due to vaccination [27], it is still highly prevalent in other areas, affecting up to one-third of dialyzed children [30, 31]. Almost 50% of children undergoing RTPL without a history of wild type infection or vaccination developed varicella with significant morbidity and mortality, whereas the incidence and severity of varicella was much lower in the immunized children [21]. In addition, several individual cases highlight the risk of vaccine-preventable infections. Measles [32, 33, 34], varicella [21, 35], or influenza [36] were responsible for significant morbidity and mortality after RTPL. *Hemophilus influenzae* type b and *Streptococcus pneumoniae* caused peritonitis in children on peritoneal dialysis [27].

A prospective study from our center covering more than a decade showed a generally low prevalence of vaccine-preventable diseases [27] based on two observations: firstly, a low prevalence of these infections among healthy children (and the patients' siblings) [37] and secondly, a high immunization rate producing detectable serum antibodies. In contrast to this report are the observations in an era of waning herd immunity where measles and other infections did not only emerge, but also presented with non-specific or atypical symptoms and a severe course [34].

The safety, immunogenicity, and clinical efficacy of available vaccines

A broad array of vaccines are currently available and recommended for children with CRF. The majority of previous reports focused on the safety and short-term immunogenicity [28, 29, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55], whereas data on the long-term clinical efficacy are rare [21, 27, 56].

Safety

Vaccination in children with CRF carries two potential risks, i.e., rejection after RTPL and live vaccine-induced infectious disease after RPTL. Killed or component vaccines have not shown any deleterious effect on renal function in children on conservative treatment or after RTPL; in particular, there was no evidence of an increased rate of graft rejection and the efficacy of dialysis was not affected in children on either peritoneal or hemodialysis [27, 38, 39, 40, 41, 42, 43, 44, 45, 48, 49, 50, 51, 52, 53, 54, 55].

Live virus vaccines have also been documented as safe in children on conservative treatment or on dialysis [21, 27, 28, 29, 46, 47, 56]. Most guidelines do not recommend live virus vaccines after RTPL. Two studies, however, reported live virus vaccination after RTPL: Zamora et al. [57] immunized 17 children against varicella; only 1 child had mild vaccination varicella and there was no evidence of graft rejection or impairment of renal function. Rand et al. [58] vaccinated 18 children after *liver* transplantation against measles without any complications attributable to the vaccine. There is also personal experience with live vaccines after RTPL, as a few of our adolescent transplant patients were given a booster vaccination against measles, mumps, and rubella on the occasion of "routine" vaccination at school (against our current recommendations). None of the patients suffered any adverse effects.

In summary, vaccination in children with CRF and after RTPL appeared to be safe, apart from local reactions or a transiently raised temperature, as observed in healthy children. There is no evidence that vaccination led to reactivation of an underlying immune-related renal disease in children with CRF or to rejection in children after RTPL. In addition, vaccination did not—as sometimes feared by parents or patients—aggravate CRF, i.e., accelerate decline in renal function. A recent publication on children with idiopathic nephrotic syndrome (and normal renal function) apparently showed a risk of relapse after meningococcal C conjugate vaccination; there was, however, bias and the conclusion was not clear [59].

Immunogenicity

Children with CRF generally produce detectable and protective serum antibodies to primary vaccinations with killed or component vaccines and live virus vaccines, as listed in Table 1: diphtheria [38, 40], tetanus [38, 40], pertussis [38], inactivated poliomyelitis [38, 42], hepatitis B [27, 43, 44, 45], measles [27, 46, 47], varicella [21, 27, 28, 29, 56], influenza [48, 49, 50], *Hemophilus influenzae* type b [51, 52], and *S. pneumoniae* [27, 53, 54, 55]. Also, administration of boosters after RTPL induced a significant antibody response: diphtheria [39, 41] and tetanus [39, 41].

There are, however, two barriers towards optimal protection. Firstly, some children on dialysis and after RTPL may not respond optimally, and not as well as children on conservative treatment, to primary vaccination, e.g., hepatitis B, influenza, and *S. pneumoniae*, i.e., they produce lower specific serum antibodies [45, 50, 55]. This problem could be overcome in some patients by repeated vaccinations (with increasing dose) [27, 45]. Secondly, vaccine serum antibodies in children with CRF have a

Table 1 Recommended immunizations in children with chronic renal failure in Zurich, Switzerland (2003) (*RTPL* renal transplantation)

Vaccination/infection	Selection of patients	Schedule	Remarks
Diphtheria-tetanus-pertussis (acellular)	All	2, 4, 6, 12–15 months; 5, 10 years	
Poliomyelitis (inactivated)	All	2, 4, 6, 12–15 months; 5, 10 years	
Measles-mumps-rubella	All	1st dose at 12 months, 2nd dose >1 month later	Live virus: if possible prior to RTPL (in selected patients boosters or even primary vaccination after RTPL)
Hepatitis A	Hepatitis C or liver disease	2 doses within 6 months	
Hepatitis B	All	3 doses within 6 months (0, 1, 6)	<10 years: 5 μg per dose; >10 years: 10 μg per dose. 4th or 5th dose (with doubling the dose) if titer <100 IE/ml
Varicella	Negative history of wild-type infection and negative IgG	1st dose at $\geq$12 months	Live virus: if possible prior to RTPL (in selected patients boosters or even primary vaccination also after RTPL). 2nd dose if 2 months after 1st vaccination IgG negative
Influenza	All on transplant waiting list and after RTPL	1 annual dose in autumn	According to yearly up-to-date recommendation of Governmental Office of Public Health
Hemophilus influenzae type b (conjugate)	All	2, 4, 6, 12–15 months; >2 years: 1 dose	In patients >5 years only, if IgG negative
Streptococcus pneumoniae	Patients on peritoneal dialysis or nephrotic-range proteinuria	<2 years: 2, 4, 6, 12–15 months; >2 years: 2 doses (0, 2 months) plus 1 dose of 23-valent	7-valent conjugate vaccine. >2 years: in addition 23-valent polysaccharide antigen

tendency to wane over a short period of time, i.e., 6–12 months [27, 41, 42, 45, 51, 52, 54, 56]. Therefore, repeated measurement of serum antibodies with appropriate revaccination has been recommended [17, 27, 45, 51, 54].

Clinical efficacy

There are several methodological difficulties in the assessment of the clinical efficacy of vaccinations in children with CRF. The proof of vaccine efficacy is the absence of disease, which can only be confirmed in large cohort studies, but not in individuals. Only a few prospective or observational studies have investigated the clinical efficacy of specific vaccinations. Broyer et al. [21] clearly demonstrated the benefit of varicella vaccination prior to RTPL, and this was confirmed by other studies [27, 29, 56]. Although a few vaccinees developed varicella after RTPL, the course was mild and renal graft function was not affected. Hepatitis B has almost "disappeared" in those countries where the vaccine has been easily available [27].

These observations provide some evidence that the implementation of various vaccines has contributed significantly, at least in the western hemisphere, to the low prevalence of vaccine-preventable diseases among children with CRF. Another explanation for the low prevalence among patients is the low prevalence of these infections—with the exception of varicella—among healthy children (and the patients' siblings) in the western world [60]. There is, however, a re-emergence of infections, e.g., measles, with decreased vaccination rate in the general populations [34].

There were also apparent vaccination failures. Children on peritoneal dialysis developed peritonitis caused by *S. pneumoniae* or *Hemophilus influenzae* type b despite the presence of serum antibody titers [27]. Serum antibody titers considered to be protective for healthy children may not prevent infections in children with CRF, and the concentration of specific antibodies in the peritoneal fluid may not be sufficient.

The implementation of the recommended immunization guidelines

The immunization rate in the general pediatric population is often moderate, i.e., 80% or less, as reported in healthy children in the United States [61], Switzerland [60], and our local community [62]. Some vaccine advisory committees recommend a reminder/recall (R/R) system by vaccination providers to increase vaccination rates [63]. The immunization schedule currently recommended at the University Children's Hospital Zurich, Switzerland is given in Table 1. Due to the low prevalence of tuberculosis in Switzerland, the Swiss Health authorities do not recommend BCG vaccine for residents in Switzerland.

Administration of the vaccines

Children with CRF are often looked after by a multidisciplinary team including several physicians (e.g., general practitioner, pediatrician, nephrologist, urologist). Vaccinations might be overlooked as "minor" problems compared with growth, nutrition, dialysis, and social difficulties. In addition, some parents and patients also either perceive an associated risk of vaccinations—e.g., measles

and autism/inflammatory bowel disease or hepatitis B and multiple sclerosis—or fear that vaccinations may aggravate CRF or induce a rejection of the renal graft. We recently reported a high immunization rate (almost 100%) in our center based on two factors [27]. Firstly, the renal team was responsible for the administration and surveillance—at least annually in October on the occasion of the influenza vaccine—of the vaccination schedule. Secondly, the renal team provided repeated information—for parents, patients, and all involved professionals—on both the risks of systemic infections on dialysis and after RTPL, and the potential protection induced by the available vaccines.

Preventive strategies in children with CRF also comprise an extended immunization schedule of their siblings and household contacts, including not only the standard primary vaccines, but also varicella, influenza, and *S. pneumoniae*. As these family members are vaccinated by their local physicians (either pediatrician or general practitioner), good communication and documentation are mandatory.

Running out of time before RTPL

Some children start dialysis at an early age during infancy or even as neonates. These young children aim for early RTPL, which is performed in many centers at 2 years of age or even younger. Therefore, the available time for administering all the primary vaccines—in particular all live vaccines—before the introduction of renal replacement therapy, either dialysis or RTPL, may be short. If the topic of vaccination is introduced early to the parents, vaccination can be completed by 15–18 months of age. As the immunogenicity of some vaccines can be impaired by dialysis, repeated (and time-consuming) vaccinations might be necessary to induce protective serum antibody titers. Thus, it might be justified to delay RTPL in individual cases for 1–2 months to revaccinate the child.

Vaccination after RTPL

Long-term graft survival has continuously improved in pediatric recipients [22, 23, 25, 26]. Thus, a substantial part of the regular immunization schedule, in particular boosters, will be administered to immunocompromised children with a functioning graft. These patients—and their caregivers—require careful information on the potential benefits and risks. Killed or component vaccines can be administered safely and effectively after RTPL.

Two issues are still unsolved. Firstly, attenuated live vaccines are contraindicated after RTPL, according to most guidelines based on the potential risk of inducing life-threatening infections. The data base, however, is poor. Only two publications—apart from anecdotal reports—studied live vaccines after solid organ transplantation, either varicella after RTPL [57] or measles after liver transplantation [58], and reported a safe and effective administration. However, live virus vaccines in individual cases after RTLP can only be endorsed when very specific indications are present where the benefit significantly outweighs the risk, e.g., in an era of low herd immunity. Measles represents a special risk as, in contrast to varicella, no effective treatment is available [34]. There is doubt that any prospective study on live vaccines after RTPL would get ethical approval.

Secondly, healthy pediatric vaccinees have a good immune memory and do not require a booster when the titer, e.g., of hepatitis B, decreases. Whether this is also true for children with CRF and after RTPL is not clear. Repeated measurement of serum antibodies with "appropriate" boosters if titers have declined has been recommended [17, 27, 45, 51, 54]. The "appropriate" schedule (annually, biannually?) remains open to debate.

Outlook and future directions

Continuous updating of the vaccination schedule is mandatory. Since 2001, the inactivated poliomyelitis vaccine has replaced the oral vaccine, and the conjugate pneumoccocal vaccine has been introduced. Unfortunately, vaccinations against cytomegalovirus, Epstein-Barr virus (EBV), BK (polyoma) virus, hepatitis C, or *Pneumocystis carinii*, causing serious and life-threatening infections in children with CRF and after RTPL, are not yet available. There is, however, an ongoing study of an EBV vaccine in pediatric patients awaiting solid organ transplantation.

Peritoneal dialysis and hemodialysis cause a disruption of the cutaneous barrier of infections with subsequent risk of bacteremia, exit-site infections, or peritonitis, the most common pathogens being staphylococci (*S. aureus or* coagulase-negative staphylococci) [64, 65, 66]. A new vaccine against *S. aureus* has emerged. Whereas previous vaccines consisting of inactivated whole cells or staphylococcus toxoid had been unsuccessful [67, 68], a new conjugate vaccine conferred at least transient immunity against *S. aureus* bacteremia in an adult hemodialysis population [69].

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